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Bidirectional modulation of sensory cortical excitability by quadripulse transcranial magnetic stimulation (QPS) in humans

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HIGHLIGHTS

- The newly designed quadripulse transcranial magnetic stimulation (QPS) was applied to the study of long-lasting sensory cortical excitability changes in humans.
- Sensory cortical excitability was modulated by QPS over the primary motor cortex or dorsal premotor cortex, but not by QPS over the primary sensory cortex itself.
- QPS might be a useful method in studies of heterotopic long-term potentiation/depression (LTP/LTD)-like effects in humans.

ABSTRACT

Objective: Quadripulse transcranial magnetic stimulation (QPS) is a newly designed patterned repetitive transcranial magnetic stimulation (TMS). Previous studies of QPS showed bidirectional effects on the primary motor cortex (M1), which depended on its inter-stimulus interval (ISI): motor evoked potentials (MEPs) were potentiated at short ISIs and depressed at long ISIs (homotopic effects). These physiological characters were compatible with synaptic plasticity. In this research, we studied effects of QPS on the primary sensory cortex (S1).
Methods: One burst consisted of four monophasic TMS pulses at an intensity of 90% active motor threshold. The ISI of four pulses was set at 5 ms (QPS-5) or at 50 ms (QPS-50). Same bursts were given every 5 s for 30 min. QPS-5 and QPS-50 were performed over three areas (M1, S1 and dorsal premotor cortex (dPMC)). One sham stimulation session was also performed. Excitability changes of S1 were evaluated by timeline of somatosensory evoked potentials (SEPs).
Results: QPS-5 over M1 or dPMC enhanced the P25–N33 component of SEP, and QPS-50 over M1 depressed it. By contrast, QPSs over S1 had no effects on SEPs.
Conclusions: QPSs over motor cortices modulated the S1 cortical excitability (heterotopic effects). Mutual connections between dPMC or M1 and S1 might be responsible for these modulations.
Significance: QPSs induced heterotopic LTP or LTD-like cortical excitability changes.

1. Introduction

Most long-term effects induced by non-invasive brain stimulation techniques in humans have been focussed on the motor cortical homotopic effect, that is, aftereffects on the primary motor cortex (M1) by stimulation over M1 itself (Chen et al., 1997; Berardelli et al., 1998; Huang et al., 2005, 2011; Gilio et al., 2009). A newly designed quadripulse transcranial magnetic stimulation (QPS) has also been applied to study homotopic effects after stimulation over M1 (Hamada et al., 2007a,b, 2008a,b). They showed bidirectional cortical plastic and metaplastic changes as predicted by the Bienenstock–Cooper–Munro (BCM) rule (Bienenstock et al., 1982).

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Several investigators have also studied long-term effects on the primary sensory cortex (S1) by repetitive transcranial magnetic stimulation (rTMS), theta burst stimulation (TBS) or direct current stimulation (tDCS) over M1 (heterotopic effect). They showed long-lasting effects on somatosensory evoked potential (SEP) (Enomoto et al., 2001; Ishikawa et al., 2007; Kodama et al., 2009), perception or pain (Satow et al., 2003; Matsunaga et al., 2004; Tamura et al., 2004; Saitoh et al., 2006; Hirayama et al., 2006; Kodama et al., 2009). The effects on S1 by S1 stimulation (homotopic effect) were controversial. Some articles reported considerable effects (Dieckhöfer et al., 2006; Ishikawa et al., 2007; Katayama and Rothwell, 2007; Katayama et al., 2010) and others reported no or only limited homotopic effects (Enomoto et al., 2001; Satow et al., 2003; Hirayama et al., 2006). Several previous investigations also studied effects of premotor cortex (PMC) stimulation on S1. The SEP was not affected by rTMS over PMC (Enomoto et al., 2001; Urushihara et al., 2006; Hosono et al., 2008). In summary, according to the long-lasting effects on S1, the heterotopic effects by stimulation over M1 and PMC are consistent in previous studies, but the homotopic effects by sensory cortical stimulation are inconsistent.

Based on these previous studies, we hypothesised that the heterotopic effects on S1 should be induced by QPS over M1, but not over dorsal PMC (dPMC). We also would like to know whether or not QPS has homotopic effects on S1. To solve these issues, in this article, we studied the sensory cortical effects by QPSs over several cortical areas using SEPs.

2. Methods

2.1. Subjects

Eleven right-handed healthy volunteers aged 32–55 years (mean, 39.6 ± 7.2 years) participated in this study. None of them had neurological or psychiatric disorders, head injuries and alcohol or drug abuse. Ten subjects participated in all the experiments and the other subject only in QPSs over M1. In each subject, two successive experiments were separated by at least 1 week. Written informed consent was obtained from all the subjects before the experiments. The protocol was approved by the Ethics Committees of Fukushima Medical University and the University of Tokyo. No adverse effects were noted in any individuals.

2.2. QPS stimulation

Prior to QPS, the active motor threshold (AMT) was measured by single-pulse transcranial magnetic stimulation (TMS) during a slight voluntary contraction of the right first dorsal interosseous (FDI) muscle. The coil was placed over the hot spot for the FDI. We used a specially designed figure-of-eight coil of 9-cm external diameter whose handle was attached vertically to the connecting point of the wings. The direction of induced current in the brain was adjusted as posterolateral to anteromedial at a 45° angle. Surface EMG was recorded from the right FDI muscle with an active electrode placed over the muscle belly and a reference electrode over the metacarpophalangeal joint of the index finger. Responses were amplified (Neuropack μ, Nihon-Kohden, Japan) through filters set at 100 Hz and 3 kHz and stored at a sampling rate of 10 kHz, and analysed offline (TMS bistim tester; Medical Try System, Japan). The mean (±standard error) AMT was 38.0% (±0.6) of the maximum stimulator output.

In QPS, the coil was connected with four magnetic stimulators through a special connecting device (MagStim 200^2; The MagStim Co. Ltd., UK), as previously reported (Hamada et al., 2007a,b, 2008a,b). During QPS, subjects lay on a comfortable reclining chair, with the target muscle relaxed. We set a large pillow under the subject's head on a reclining chair to fix the coil stably. One burst consisted of four monophasic TMS pulses at the same intensity (90% AMT) and the same bursts were given every 5 s (inter-burst interval). Interstimulus intervals (ISIs) of four pulses were set at 5 ms (QPS-5) or at 50 ms (QPS-50), which induced the most powerful LTP-like and LTD-like effects on M1, respectively (Hamada et al., 2007a,b, 2008a,b). QPS was given over three sites: the hot spot for the FDI muscle (M1), 3 cm anterior to M1 (dPMC) (Siebner et al., 2003) and C3′ (2 cm behind C3 of the International 10–20 system) which is usually used for recording median nerve SEPs. Each session consisted of 360 bursts (1440 pulses) for 30 min.

For the sham stimulation, we used the 'realistic sham' technique. This method was used in previous studies (Okabe et al., 2003; Nagel et al., 2008) and had considerable placebo effects (Hamada et al., 2008a,b). We placed a coil over the scalp connecting to an uncharged stimulator to give a pressure sensation similar to real stimulation. To mimic real QPS, stimulation noises of QPS-50 were given by firing another stimulator through a non-stimulating coil beside the subject's head, and skin sensation was given with an electric stimulus through the electrodes placed directly over the scalp at the same time. Any sham method has pros and cons (Borckardt et al., 2008) and it is difficult to mimic correctly the muscle twitch of real stimulation in a sham procedure. The sham technique with electrodes placed directly on the scalp, however, was useful even though the stimulation was not identical to rTMS (Mennemeier et al., 2009).

In every subject, the order of seven QPS sessions (sham stimulation, QPS-5 and QPS-50 over three cortical areas) was randomised to avoid the order effect.

2.3. SEP

For SEP recording, we stimulated the right median nerve at the wrist at 2 Hz. The recording electrode was placed over the hand

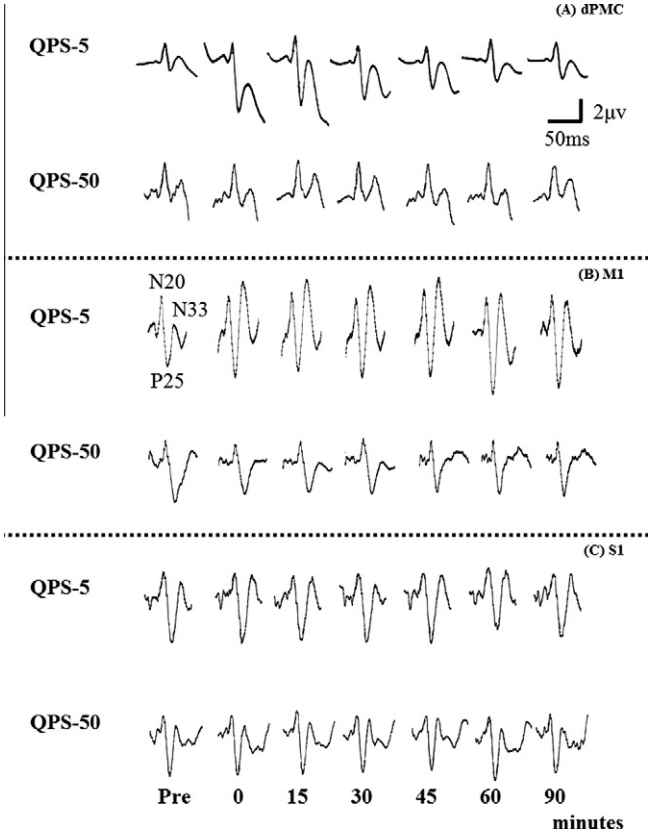

Fig. 1. Typical SEP waveforms before and after QPSs. (A) shows SEPs for the dPMC stimulation experiment, (B) for M1 stimulation and (C) for S1 stimulation. The upper rows are those for QPS-5 and the lower for QPS-50 in each site of stimulation.